REMARKS

Prior to entry of the amendments presented above, claims 39-76 were pending the application. Claims 66-70 and 72-76 were withdrawn from consideration. Claims 45, 59-65, 68, 69 and 71-71 have been canceled, and claims 39-42, 44-58, 66, 67, 70, and 74-76 have been amended. Claims 77 and 78 have been added. The claim amendments and added claims are fully supported by the specification and claims as originally filed and, in particular, Example 1.

In the May 6, 2008 Office Action, claims 39-65 and 71 were rejected under 35 USC § 112, second paragraph, as indefinite, and under § 112, first paragraph, for lack of written description. Claims 39-65 also were rejected under 35 USC § 112, first paragraph, for lack of enablement. Claims 39 and 71 were rejected under 35 USC § 102(b) as anticipated by Frazer, and claims 39, 44, 49-50, 52-53 and 71 were rejected under § 102(b) as anticipated by Zolotukhin. Claims 39-40, 44, 49-55 and 71 were rejected under § 103(a) as obvious over Seed in view of Rosenberg. The specific grounds for rejection, and applicant's response thereto, are set forth in detail below.

Rejections under 35 USC § 112, second paragraph

Claims 39-65 and 71 are rejected under 35 USC § 112, second paragraph, as indefinite Specifically, the Examiner asserts that in claim 39 "it is unclear if the selected phenotype set forth [in the last three lines of the claim] is the same selected phenotype recited in lines 2-4 of this claim which recites wherein the **selected phenotype** is "of a **different quality** than that conferred by a parent polynucleotide that encodes the same polypeptide." In claims 41-43 the Examiner asserts that the term "reporter gene" lacks antecedent basis, and in claim 56 the Examiner asserts that the term "the tandem repeat of each of the synthetic constructs" lacks antecedent basis. The Examiner also states that claim 56 improperly depends from a canceled claim. Applicant respectfully traverses.

With respect to claim 39, applicant has amended the claim in a manner that moots the rejection. With respect to claims 41-43 applicant respectfully notes that these claims now depend from claim 40, which specifically recites a reporter protein (the Office Action refers to a "reporter gene" but this term does not appear in claims 41-43). In claim 54, applicant respectfully does not understand the rejection. Claim 39, from which claim 54 depends, recites "separately introducing into the test mammals individual *synthetic constructs*, each of which

comprises a regulatory polynucleotide operably linked to a *tandem repeat* " (emphasis supplied). It is clear therefore that claim 39 refers to synthetic constructs that contain tandem repeats. Applicant has amended claim 56 to correct the dependency. Accordingly, applicant respectfully requests withdrawal of the rejections.

Rejections under 35 USC § 112, first paragraph

Claims 39-65 and 71 are rejected under § 112, first paragraph, for lack of written description, and claims 39-65 also are rejected under § 112, first paragraph, for lack of enablement. Specifically, the Examiner asserts that the specification fails to describe sufficient members of the genus of selected phenotypes to provide a written description of that genus. The Examiner also asserts that the specification fails to enable the full scope of selected phenotypes or organisms that display the phenotype. Applicant respectfully traverses.

With respect to the rejection for lack of written description, applicant respectfully submits that a person skilled in the art reading the instant specification readily would comprehend that the specification describes a representative number of selected phenotypes sufficient to demonstrate that the inventor had possession of the claimed invention. Nevertheless, without acquiescing in the rejection, and merely to move the application towards allowance, applicant has amended the claims to specify that the "selected phenotype" is an immune response to a target antigen. This is fully described at, for instance, Example 1 of the specification. One skilled in the art readily would understand that the inventor had full possession of the claimed methods that permit preparation of polynucleotides that can be used to modulate an immune response to a target antigen in a mammal. Accordingly, withdrawal of the rejection respectfully is requested.

With respect to the rejection for lack of enablement, applicant respectfully submits that a person skilled in the art readily would be able to make and use the entire scope of the claimed invention without undue experimentation. Nevertheless, without acquiescing in the rejection, and merely to move the application towards allowance, applicant has amended the claims to specify that the "selected phenotype" is an immune response to a target antigen. Methods for preparing polynucleotides that can be used to modulate an immune response in a mammal are fully enabled by the specification, for instance in Example 1. Moreover, applicant appends hereto a Declaration Pursuant to 37 CFR § 1.132 by Professor Ian Frazer, the inventor of the

claimed invention, that describes how the methods described in the specification were used to identify codon preferences that were used to successfully generate an improved immune response in a mammal against an HPV E7 protein. The data provided by the Frazer declaration further demonstrate that the claimed methods fully comply with the enablement requirement of § 112, first paragraph. Accordingly, withdrawal of the rejection respectfully is requested.[1]

Rejections under 35 USC § 102(b)

Claims 39 and 71 are rejected under 35 USC § 102(b) as anticipated by Frazer, and claims 39, 44, 49-50, 52-53 and 71 are rejected under § 102(b) as anticipated by Zolotukhin. Applicant respectfully traverses.

It is axiomatic that, for a reference to be anticipatory, it must teach each and every limitation of the claims. In the instant case, the claims are directed to methods that permit preparation of polynucleotides that can be used to modulate an immune response to a target antigen in a mammal, and to methods of modulating an immune response to a target antigen. Neither of the cited references describes methods of preparing polynucleotides that can be used to modulate an immune response in a mammal, nor does either reference describe methods of modulating an immune response. Accordingly, neither reference teaches each and every limitation of the claimed invention and withdrawal of the rejection respectfully is requested.

Rejections under 35 USC § 103(a)

Claims 39-40, 44, 49-55 and 71 are rejected under § 103(a) as obvious over Seed in view of Rosenberg. Specifically, the Examiner argues that Seed teaches a method of replacing low usage codons with synonymous high usage codons to provide higher translation efficiencies but does not teach methods of measuring iso-tRNA abundance in cells using tandem repeats. Rosenberg is cited as teaching a method of testing translational efficiency of individual codons using such repeats. The Examiner therefore concludes that it would have been obvious to combine Seed and Rosenberg to produce a DNA construct where synonymous codons are replaced to produce higher translational efficiency. Applicant respectfully traverses.

[1] Professor Frazer's declaration was executed in Australia, which is many hours ahead of US time. As a result, the declaration is dated November 7, 2008, although it was executed on November 6, 2008, US time.

The instant claims are directed to methods that permit preparation of polynucleotides that can be used to modulate an immune response in a mammal, and to methods of modulating an immune response in a mammal. Neither of the cited references teaches or suggests such methods. Rather, the cited references are directed simply to methods of optimizing codon usage in cells, and not to modulating an immune response in a whole mammal.

An immune response in an animal can be induced by delivering a gene to that animal, and expression of the gene results in an immune response to the polypeptide encoded by the gene. Seed and others had developed tables of preferred codons for optimizing gene expression in isolated cells, and had assumed that this codon preference applied to all cell types in an organism. This is incorrect, however, as the present inventor's prior work has shown that different cells in a multicellular organism exhibit different translational efficiencies for the same codon. Moreover, when a gene is delivered to a whole animal to generate an immune response, it is not known what cells are important for expression of the gene in order to optimize the immune response in a desired way, nor is it clear that the nature of the immune response is related to translation efficiency. Accordingly, the tables of preferred codons developed, for example, by Seed, are not useful for optimizing the immune response in a whole animal.

The methods of the present invention address the deficiencies of the methods of Seed and Rosenberg and others by providing methods that permit modification of an immune response to target antigen in a mammal by identifying synonymous codon preferences that produce a desired modified immune response. The methods can be used to develop codon preferences for any target antigen, as described in the Frazer declaration. Moreover, the codon preferences for the HPV E7 antigen, as described in Appendix C to the Frazer declaration, are quite distinct from the preferences identified by Seed. These distinctions are shown in the table set forth below:

aa	Preferential codon usage as predicted by Seed for mammalian cells in general	Experimentally determined codon immune response preferences in test mammals
Ala	GCC >> (GCG, GCT, GCA)	GCT > GCC > (GCA GCG)
Arg	CGC >> (CGA, CGT, AGA, AGG, CGG)	(CGA, CGC, CGT, AGA) > (AGG, CGG)
Asn	AAC >> AAT	AAC > AAT
Asp	GAC >> GAT	GAC > GAT
Cys	TGC >> TGT	TGC > TGT
Glu	(GAA, GAG)	GAA > GAG
Gln	CAG >> CAA	CAA = CAG
Gly	GGC > GGG > (GGT, GGA)	GGA > (GGG, GGT, GGC)
His	CAC >> CAT	CAC = CAT
Ile	ATC > ATT > ATA	ATC >> ATT > ATA
Leu	CTG > CTC > (TTA,CTA, CTT, TTG)	(CTG, CTC) > (CTA, CTT) >> TTG > TTA
Lys	AAG >> AAA	AAG = AAA
Phe	TTC >> TTT	TTT > TTC
Pro	CCC >> (CCG, CCA, CCT)	CCC > CCT >> (CCA, CCG)
Ser	AGC > TCC > (TCG, AGT, TCA, TCT)	TCG >> (TCT, TCA, TCC) >> (AGC, AGT)
Thr	ACC >> (ACG, ACA, ACT)	ACG > ACC >> ACA > ACT
Tyr	TAC >> TAT	TAC > TAT
Val	GTG > GTC > (GTA, GTT)	(GTG, GTC) > GTT > GTA

Nothing in either Seed or Rosenberg, alone or in combination, teaches or suggests that the immune response to a target antigen in a mammal can be modified by identifying preferred synonymous codon usage for a target antigen. Indeed, as shown in the table above, Seed teaches away from the present invention by identifying codon preferences that in several instances are quite different from those identified using the instantly claimed invention. Accordingly, no *prima facie* case of obviousness exists and withdrawal of the rejection respectfully is requested.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully submit that the application is in condition for allowance. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the undersigned to expedite prosecution of the application.

The Commissioner is hereby authorized by this paper to charge any fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-3840. **This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).**

Respectfully submitted,

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